

REMARKS

The above amendments have been provided based on the format described at 1265 Off. Gaz. Pat. Office 87 (December 17, 2002) and as authorized by Deputy Commissioner for Patents, Stephen Kunin on January 31, 2003.

Support for the amendment to page 1 of the specification expressly claims the benefit of priority as supported by the Application Data Sheet as filed October 25, 2001. The paragraph on page 11 has been amended to expressly relate to Figures 1A through 1C instead of Figure 1. The paragraph bridging pages 23-24 has been amended with respect to the trademark "SEQUENASE". The paragraph bridging pages 36-37 has been amended to introduce a Sequence Identifier No. to comply with 37 CFR 1.821 through 1.825.

Claims 1 and 17 have been amended to correct a clerical error in the previous recitation of "mRNA/cDNA" hybrids. The text of the claim has been amended to be directed to hybrids of a "single stranded polynucleotide" and cDNA as supported by the claim as filed. Applicants believe that the term "single stranded polynucleotide" is broader than "mRNA". The claims have also been amended to incorporate the "one or more than one" phrase from the start of the claims into the body of the claims as the context requires.

Claim 9 has been amended to use alternate language for the same subject matter without altering the scope of the claim. Support is provided by the claim as originally filed.

Claim 10 has been amended to with respect to the recitation of "aRNA/DNA" by express language directed to subject matter inherently present in the claim. No change in claim scope has occurred. Support is provided by the claim as originally filed.

No new matter has been introduced, and entry of the amendments is respectfully requested.

Specification

The disclosure has been objected to because Figure 1C is allegedly not described. Page 11 of the application has been amended above to address this objection.

The use of the trademark “SEQUENASE” in the paragraph bridging pages 23-24 has been amended to be in capital letters along with the use of a trademark designation. No generic terminology appears appropriate at this time.

A submission in compliance with the sequence rules is enclosed herewith. Page 37 has been amended as noted above to incorporate Sequence Identifiers as needed. No new matter has been introduced.

Rejection under 35 U.S.C. § 112

Claims 1-32 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for the use of various language. Applicants have carefully reviewed the statement of the rejection and believe that the claims are definite for the following reasons.

As an initial matter, Applicants refer to the Memorandum dated January 17, 2003 from Stephen Kunin, Deputy Commissioner for Patent Examination Policy at the U.S. PTO (copy attached). The Memorandum sets forth a clarification and immediate implementation of policy with respect to rejections under 35 U.S.C. § 112, second paragraph. Of particular relevance to the instant rejection is the statement that

“[I]f the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. § 112, second paragraph would be appropriate.”

Applicants believe that this means that if an artisan of ordinary skill can interpret the metes and bounds of the claim to avoid infringement, no rejection under 35 U.S.C. § 112, second paragraph is proper.

Additionally, Applicants point out the emphasis in the Memorandum on considering “the claim as a whole” as opposed to a focus on particular words or phrases in a claim. This is discussed further on page 2, first full paragraph, of the Memorandum which includes an example concerning the use of the phrase “such as” in a claim. This example is used to modify previous practice as set forth at MPEP 2173.05(d), upon which the instant rejection is based at least in part.

Turning to the statements of the rejection, the rejection of claim 9 based on the recitation of “combinations thereof” is traversed because an ordinary artisan would recognize that the phrase refers to combinations of exonuclease deficient Klenow and/or Taq polymerase activities as recited in claim 9. Therefore, no amendment was necessary to obviate this rejection. However, and because the same concept can be encompassed by alternative language without altering claim scope, claim 9 has been amended above. Withdrawal of this rejection is respectfully requested.

Claim 10 has been rejected based on the phrase “the aRNA/DNA hybrids”. Applicants strongly traverse because claim 1, from which claim 10 depends in all cases, expressly defines “aRNA” as “amplified RNA” while lines 16-20 on page 47 describe how the aRNA is used to generate a DNA strand by reverse transcription. As would be recognized to the ordinary artisan, reverse transcription results in a duplex, aRNA/DNA hybrid. Claim 10 has been amended to include this inherent result of reverse transcription without altering the scope of the claim. The language is thus not unclear, especially in light of the directive in the above described Memorandum. Withdrawal of this rejection is respectfully requested.

Claims 10-16 have been rejected based on the term “and/or”. Applicants note that the use of the term must be considered in context within the claim as a whole, which has been amended to recite “acts of the method” in the last section of claim 10. This does not change the parts of claim 10 to which the last section refers. The term “and/or” must be viewed within the amended phrase in which the term is used: “wherein the above annealing, synthesizing, annealing, forming and/or transcribing acts of the method are optionally repeated”. The ordinary artisan would recognize that the phrase means that one or more of the acts recited in claim 10 may be “optionally repeated” and still be encompassed by the claim. No indefiniteness is present, and withdrawal of the instant rejection is requested.

Claims 17-30 and 32 have been rejected based on the recitation of “the mRNA/cDNA hybrids” in claim 17. This is addressed below in combination with claim 1.

Claims 17-30 and 32 have also been rejected based on the recitation of “the aRNA/DNA” in claim 17. Once again, Applicants note that earlier portions of claim 17 describe the use of reverse transcription which would be recognized by an ordinary artisan as resulting in duplex hybrids encompassed by the terms quoted above. Claim 17 has been amended to include this

inherent result of reverse transcription without altering the scope of the claim. The language is thus not unclear, and withdrawal of this rejection is respectfully requested.

Claims 1-16 and 31 have been rejected based on the recitation of “said sequences” in claim 1. As evident from a review of the context of section a)i) in claim 1, the term is used in the larger phrase “wherein said sequences are operably linked to a promoter region”. Therefore, “said sequences” would be recognized by the ordinary artisan as referring to the “sequences present in said target polynucleotide”. The ordinary artisan would not consider the possibility of the reference being to the “RNA sequences” in line 1 of the claim because it makes no sense in the context of the claim that RNA would be “operably linked to a promoter region”. Therefore, and consistent with the standard set forth in the above described Memorandum, claim 1 is definite, and no amendment is necessary.

Claims 1-32 have been rejected based on the recitation of “aRNA” despite the fact that *claim 1 clearly indicates that it is used to denote* “amplified RNA”. The statement of the rejection appears to recognize this but then continues to assert that the term may be interpreted as referring to “antisense RNA”. Applicants strongly traverse because it is well settled law that applicants may be their own lexicographers (see MPEP 2173.01 and the case cited therein). In the instant case, independent claims 1 and 17 both expressly indicate that “amplified RNA” may be abbreviated as “aRNA”. Therefore, all dependent claims, which necessarily have all the limitations of the independent claims from which they depend, must necessarily have the same equivalence between the term and the abbreviation. No indefiniteness is raised merely because the same abbreviation may be used for another term where the claims expressly set out the meaning of the abbreviation. Therefore, Applicants strongly traverse this rejection, especially in light of the Memorandum described above, and submit that this rejection should be withdrawn.

Claims 1-32 have been rejected based on the recitation of “random primer region”. Once again, the term should be viewed in the context of the claim 1 phrase in which it occurs: “a plurality of second oligonucleotides comprising a random primer region”. Therefore, “random primer region” would be recognized by the ordinary artisan as referring to a region of the “second oligonucleotides” that is a “random primer” in form. This is consistent with the statement of the rejection’s description of “random primer” being a random combination of nucleotides. Contrary to the assertion in the statement of the rejection, and because the use of “random primer region” is consistent with this description of the meaning of “random primer”,

there is no need to distinguish the terms “random primer region” and “random primer” from each other. Moreover, and given the use of “comprising” as quoted above, the “second oligonucleotides” may be a random primer, or oligonucleotides containing a random primer, or a combination of both. This follows because the language used is broad, and Applicants point out that breadth does not equal indefiniteness (see MPEP 2173.04 and the case cited therein). Therefore, Applicants strongly traverse the instant rejection and submit that it should be withdrawn.

Claims 14 and 25 have been rejected based upon the recitation of “polymerase activity comprises exonuclease deficient Klenow and Taq polymerase”. Once again, the term should be viewed in the context of the phrase in which it occurs: “DNA dependent DNA polymerase activity comprises exonuclease deficient Klenow and Taq polymerase *activities*” (*emphasis added*). An ordinary artisan would recognize that the “DNA dependent DNA polymerase activity” comprises the *activities* of both exonuclease deficient Klenow **and** Taq polymerase. It appears from the statement of the rejection that the recitation of “exonuclease deficient Klenow and Taq polymerase” is being interpreted in the alternative, despite the express use of “and” in the claims. No such interpretation was intended for the claims, and Applicants respectfully submit that the claims be interpreted based upon the language used and the context in which it occurs. This rejection should be withdrawn.

Claims 15, 16, 29, and 30 have been rejected based upon the recitation of “known primer”. Once again, the term should be viewed in the context of the phrase in which it occurs: “said third oligonucleotide comprises as known primer *sequence*” (*emphasis added*). An ordinary artisan would recognize that the term “known primer sequence” refers to a primer sequence which is known, as opposed to unknown or random. Claims 10 and 17, from which claims 15, 16, 29, and 30 depend, expressly recite that the third oligonucleotide comprises a “primer region”. An ordinary artisan would recognize that a “primer region” is composed of a “primer sequence” which may be known, unknown, or random. Accordingly, the claims are not indefinite, and this rejection should be withdrawn.

Claims 1 and 17 have been rejected based upon the recitation of “mRNA”, which occurs within the recitation of “the mRNA/cDNA hybrids”. Claims 1 and 17 have been amended to refer to the hybrids as being comprised of “single stranded target polynucleotide” and the synthesized “cDNA” to correct a clerical error in the claims. The amendment, in addition to

being directed to the broader scope of single stranded target polynucleotides (as opposed to mRNAs), also makes claim 2 more consistent with claim 1 and claim 19 more consistent with claim 17. Applicants respectfully submit that the basis for this rejection has been obviated and the rejection may be withdrawn.

Prior art rejection under 35 U.S.C. § 103

Claims 1-32 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Lin et al. (US 2002/0137709) in view of Adams et al. (USP 6,297,365 B1). Applicants have carefully reviewed the statement of the rejection as well as the cited references and respectfully traverse this rejection as failing to have provided a *prima facie* case of obviousness.

As an initial matter, the rejection appears to be based upon critical misunderstandings of what the references disclose. In the interest of clarity in the record, Applicants begin by pointing out these misunderstandings as found in the statement of the rejection. The Examiner is invited to comment with particularity on the following in the interest of the clearest possible record.

The first critical misunderstanding is seen in the allegation that Lin et al. teach the use of random primers to anneal to a first strand cDNA to synthesize a complementary second cDNA strand as required by the instant claims. In fact, Lin et al. only mentions the term “random primer” in paragraph 0099 on page 8 and in paragraph 0109 on page 10 in the context of “random primer extension” to produce radiolabeled probes. This is simply not the same as using random primers to synthesize cDNA strands as encompassed by the instant claims.

The statement of the rejection asserts that step (e) of claim 1 on page 12 of Lin et al. discloses the annealing of first strand cDNA “with a plurality of second oligonucleotides comprising a random primer region to form a population of second complexes”. This is in error because nowhere in claim 1 of Lin et al. is there any mention of the use of random primers. Moreover, the assertion is incorrect because step (c) in claim 1 of Lin et al. already describes the generation of a promoter-linked double-stranded nucleic acid molecule from the first cDNA strand. Step (d) in claim 1 of Lin et al. describes using that double-stranded molecule to synthesize mRNA fragments, and *it is these mRNA fragments that are contacted with primers* to permit the production of mRNA/cDNA hybrids in step (e). This is clearly not the same as the act

of using oligonucleotides comprising a random primer region to produce double stranded cDNA templates as recited in instant claims 1 and 17 (see sections a)iv) and a)v) of each claim).

Applicants believe that a better understanding of the method of Lin et al. would be beneficial in understanding why the instant rejection is misplaced. The general schemes for the methods of Lin et al. are shown in Figures 1 and 7 therein. As shown in Figure 1, a polyadenylated mRNA is annealed to a poly(dT) primer (*without a linked promoter*) to produce an mRNA/cDNA hybrid via reverse transcription. This hybrid is then treated with terminal transferase and dGTP to “tail” the cDNA strand of the hybrid with a poly(dG) tail. The “dG tailed” cDNA is then separated from the mRNA by denaturation and hybridized to a poly(dC) primer linked to a T7 promoter sequence. Extension of the primer gives a double-stranded cDNA molecule with the T7 promoter capable of initiating the transcription of “sense” mRNAs that are not complementary to the original polyadenylated mRNA used to generate the double-stranded cDNA. Figure 7 shows a variation of the above where the T7 transcribed “amplified mRNAs” are reverse transcribed with a poly(dT) primer (*without a linked promoter*) and further processed as described above.

The method described by Lin et al. is very different from the instantly claimed invention where the first step is reverse transcription of a starting template with a poly(dT) primer *linked to a promoter*. Contrary to the assertion concerning step (a) in claim 1 of Lin et al. on page 5 of the Office Action mailed November 7, 2002, the “promoter-linked primers” recited in step (a) are “sufficiently complementary to the **antisense** conformation” (emphasis added) of the starting nucleic acid template. Stated differently, the “promoter-linked primer” is not complementary to the starting template but rather complementary to the *antisense* of the starting template. This is wholly consistent with the method disclosed in Figures 1 and 7 of Lin et al. as described above. But the “promoter-linked primer” would not be able to prime reverse transcription from the starting template as required by the instant claims.

Applicants respectfully submit that this critical misunderstanding of the method disclosed, and apparently claimed by Lin et al., causes many of the other allegations concerning Lin et al. in the statement of the rejection to be either in error or irrelevant to the instant claims. For example, the assertion of step (b) in claim 1 of Lin et al. as disclosing reverse transcription with the “promoter-linked primer” is in error. Step (b) refers to the use of the “ii) one or more primers sufficiently complementary to the sense conformation of said nucleic acid template” as

recited in step (a) in claim 1 of Lin et al. This primer is **not promoter-linked** as shown in Figures 1 and 7 of Lin et al. and is completely different from the promoter linked primers used in the instantly claimed methods.

Other errors in the statement of the rejection include the reference to claim 5 of Lin et al., which is directed to step (c) in claim 1 of Lin et al. and the use of a promoter-linked primer with the first cDNA strand rather than the starting nucleic acid template. Contrary to the allegation in the statement of the rejection, this does not describe either the use of a promoter-linked primer as encompassed by the instant claims or the use of random primers to form double stranded cDNA as encompassed by the instant claims.

Another error is the reference to claim 13 of Lin et al., which is directed to the primers “complementary to the 5’-ends of the *sense* conformation of said nucleic acid template” (*emphasis added*). Therefore, and contrary to the statement of the rejection, the teaching does not describe the use of an oligonucleotide comprising a known primer sequence that is complementary to the 3’ region of amplified RNA as encompassed by the instant claims.

Adams et al. do not remedy the above deficiencies of Lin et al. Adams et al. do not teach the use of random primers to synthesize a duplex cDNA molecule after annealing to a first cDNA strand; and they do not teach the use of a promoter linked primer to synthesize a first cDNA strand. Additionally, neither reference teaches or suggests the use of exonuclease as recited in section a)iii) of instant claims 1 or 17.

Therefore, no combination of Lin et al. and Adam et al. is able to teach or suggest all of the limitations of the instantly claimed methods (see MPEP 2143.03 and the cases cited therein). Therefore, and assuming *in arguendo* that motivation to combine these references is present, a combination cannot lead the artisan of ordinary skill to the instantly claimed invention. Accordingly, Applicants respectfully submit that no *prima facie* case of obviousness has been presented, and this rejection may be properly withdrawn.

CONCLUSION


In light of the above discussion and traversals, Applicants believe that the claims are in condition for allowance and urge early indication to that effect. The Examiner is encouraged to contact the undersigned to expedite prosecution of the instant application.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 485772002900.

Respectfully submitted,

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